Infectious diseases have always been a major health problem throughout the world, imposing strong selective pressure on the human genome. Despite the recent development of vaccines and antibiotics, there are still nearly 15 million deaths every year attributable to the effects of infectious diseases. Although genetic studies of infectious diseases have identified important pathways involved in protective immunity, very little is known about the underlying genetic and evolutionary factors contributing to differences in susceptibility to infectious diseases at the population level. In this talk, I will discuss the importance of host genetic and epigenetic factors in shaping population differences in innate immune responses to infectious agents. I will also discuss recent findings from our lab showing that BCG can be used to reprogram hematopoietic stem cells (HSC) to generate protective innate immunity against tuberculosis. Our results indicate that targeting the HSC compartment provides a novel approach for vaccine development.